## REMARKS

Prior to the present amendment, claims 26-31, and 33 were pending. Claims 1-20, and 32 were previously canceled. By the present amendment, applicants have amended claim 27, canceled claims 29-31, and added new claims 34-35. No new matter has been added. Accordingly, claims 26-28, 33-35 are under consideration.

**Rejection under 35 U.S.C. § 112, second paragraph**

On page 2 of the office action, the examiner rejects claims 29-31 as being indefinite under 35 U.S.C. § 112, second paragraph. In response, applicants have amended the affected claims such that the respective compositions consist essentially of a component. Applicants respectfully request reconsideration and withdrawal of the rejection.

**Rejection under 35 U.S.C. § 103 over Eschenfelder and Baldwin**

On page 4 of the office action, the examiner rejects claims 26-28 and 33 as being rejected U.S.C. § 103(a) over Eschenfelder (*US 4,944,943*) and Baldwin (US *5,098,707*). The examiner asserts that "Baldwin teaches compositions *comprising* streptokinase for the treatment of vascular disease" (emphasis added). The examiner states that "Eschenfelder teaches a method for the treatment of vascular disorders, such as hemorrhoid disease, *comprising* administering a thrombolyic substance such as streptokinase to a patient *in combination with an antithrombotic substance*" (emphasis added). The examiner alleges that one of skill in the art would have

understood that a thrombolytic agent could have been formulated in the absence of any additional active components for use in a method of treating hemorrhoid disease.

Applicants respectfully disagree. "All words in a claim must be considered in judging the patentability of that claim against the prior art." *MPEP § 2143.03.* The claimed method for treating hemorrhoid disease includes administering a pharmaceutical composition "consisting essentially of" a thrombolytic protein, wherein the pharmaceutical composition is administered rectally.

Baldwin fails to disclose administering a pharmaceutical composition "consisting essentially of" a thrombolytic protein for treatment of hemorrhoid disease. The "compositions to be employed in the practice of the [Baldwin] invention whether parenteral, oral or suppository compositions *comprises an imidazole* compound in a pharmaceutically acceptable carrier" (emphasis added). See col. 23, lines 65-69 of Baldwin. Accordingly, the compositions disclosed in Baldwin require imidazole and do not read upon the claimed compositions "consisting essentially of" a thrombolytic protein. See also col. 24, lines 13-19 of Baldwin, as cited by the examiner. In addition, as acknowledged by the examiner on page 4 of the office action, Baldwin is devoid of any disclosure or suggestion of a method for treating hemorrhoid disease.

Eschenfelder fails to rectify the deficiencies of Baldwin. Eschenfelder does not disclose administering a pharmaceutical composition "consisting essentially of" a thrombolytic protein for treatment of hemorrhoid disease. Eschenfelder discloses "*a mixture* of a substance having

thrombolytic activity and of an anti-thrombolytic substance" (emphasis added). See col. 1, lines 23-25 of Eschenfelder. The passages of Eschenfelder that were cited by the examiner also require the mixture.

Accordingly, the combination of references fails to obviate the invention as it is claimed.

Moreover, contrary to the examiner's assertion, one skilled in the art would have lacked any motivation to combine the teachings and any reasonable expectation of success in arriving at the claimed method for treating hemorrhoid disease, which includes rectally administering a pharmaceutical composition "consisting essentially of" a thrombolytic protein.

For example, there was no motivation to combine the teachings and arrive at the claimed invention since both references teach compositions the "comprise" mixtures. The references in combination and individually are devoid of any teaching or suggestion of a composition "consisting essentially of" a thrombolytic protein.

Furthermore, there was no reasonable expectation of success in arriving at the claimed invention because one skilled in art at the time of the invention would not have considered rectally administering a composition "consisting essentially of" a thrombolytic protein. The Bachmann reference (submitted in the IDS filed concurrently herewith) states that "Our own experience has shown that *no or only minimal* thrombolytic activity could be measured in the plasma of patients to whom doses of 200,000 to 300,000 U. of streptokinase had been administered orally or *rectally*" (emphasis added)(sentence bridging pages 228-229 of

Bachmann). The Bachmann investigators, therefore, studied patients receiving streptokinase rectally in the form of Varidase, which Bachmann defines as a composition having streptokinase *and* streptodornase as "chief constituents" (emphasis added)(see abstract and first sentence of first paragraph on page 228 of Bachmann).

Accordingly, Bachmann not only teaches that, at the claimed invention at the time of the invention, there was no reasonable expectation of success at arriving, Bachmann further teaches that at the time of the invention, the art taught away from rectally administering a pharmaceutical composition "consisting essentially of" a thrombolytic protein.

Additional references submitted herewith also teach the absence of any reasonable expectation of success at arriving at the claimed invention. Inventive activity is required to develop rectal formulations in which the active element is a protein, such as a thrombolytic protein, because the stability of such protein may be affected by additional formulation elements and/or by proteases present at the site of administration.

For example, the Yamamoto reference discloses evidence of proteases at the rectum in Figure 3 (see page 282 of Yamamoto, submitted in the IDS filed concurrently herewith). The Yamamoto reference further states that "rectal absorption of peptide and protein drugs *is still poor* as compared with intravenous administration" (emphasis added)(see page 276, left column, lines 11-14 of Yamamoto). In addition, the Yamamoto reference explains the difficulty in developing rectal formulations: "rectal absorption of peptides is typically very low due to poor

membrane permeability characteristics and extensive hydrolysis in the rectal mucosa" (see page 296, left column, conclusion paragraph).

Lastly, applicants submit the Nisar reference (IDS filed concurrently herewith), which provides a review of available methods of treating hemorrhoids known in the art after the time of the invention. Notably, the review does not include rectally administering a pharmaceutical composition "consisting essentially of" a thrombolytic protein.

Accordingly, the claimed invention of a method for treating hemorrhoids that includes rectally administering a pharmaceutical composition "consisting essentially of" a thrombolytic protein was a surprising discovery. The cited references, individually and in combination, fail to obviate the claimed invention. The combination of references fails to read on the invention as it is claimed and the combination of references fails to provide any motivation and reasonable expectation of success for arriving at the invention. Applicants respectfully request reconsideration and withdrawal of the rejection.

**Rejection under 35 U.S.C. § 103 over Eschenfelder, Baldwin, Ivy, and Oh**

On page 12 of the office action, the examiner rejects claims 26-31 and 33 under 35 U.S.C. § 103(a) over Eschenfelder and Baldwin as applied to claims 26-28, and 33 above, and in further view of Ivy (*US 5,720,962*) and Oh (*WO 01/22935*).

Applicants believe that the claim amendments and arguments outlined above, overcome the present rejection. For example, the combination of references also fails to provide any motivation and reasonable expectation of success for arriving at the invention for the reasons provided above. The Ivy and Oh references fail to rectify the deficiencies of the combination of Eschenfelder and Baldwin.

Furthermore, the Oh reference teaches away from the claimed invention and confirms that there is no motivation to combine the references. Oh discloses that its composition is to be applied "not to the localized region, but to the palm or other particular parts of the hand" (p. 2 last paragraph to p. 3, line 7 of Oh).

Applicants respectfully request reconsideration and withdrawal of the rejection.

**Conclusion**

In view of the foregoing amendments and remarks, entry of the amendments and favorable consideration of the claims are respectfully requested. If the examiner has any questions or concerns regarding this amendment, she is invited to contact the undersigned at the telephone number listed below. If any fees are due or any over overpayment made in connection with this paper, please charge or credit our Deposit Account No.: 08-2461.

Respectfully submitted,

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